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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/775,869	02/10/2004	Ekaterina Dadachova	96700/845	1864

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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/775,869	DADACHOVA ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-19,25-33,35-37 and 41-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 5-19, 25-33, 35-37 and 41-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/26/2007 has been entered.

Claims 1-2, 5-19, 25-33, 35-37 and 41-44 are currently pending and under consideration.

The Declaration under 37 CFR 1.132 filed on April 4, 1007 by Ekaterina Dadachova is insufficient to overcome the rejection of claims 1-2, 5-19, 25-33, 35-37 and 41-44 under 35 U.S.C. 112, first paragraph as set forth in the last Office action because the Declaration does not appear to be commensurate in scope with the claimed invention. For example, the Declaration teaches experiments using whole and/ or lysed MNT1 pigmented human melanoma cells, which are described in the present application, and an anti-melanin monoclonal antibody referred to as 11B11 labeled with 188-Rhenium, wherein binding of 188Re-11B11 to MNT1 highly melanized cells was melanin-specific as lysing of the cells which makes more melanin accessible for a melanin-binding mAb resulted in increased binding. Thus, while the Declaration sets forth in vitro experiments, the Declaration does not appear to be commensurate in scope with the claimed invention which is drawn to in vivo treatment and/or imaging using a monoclonal antibody which specifically binds to melanin.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 5-19, 25-33, 35-37 and 41-44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating and/or imaging melanin containing melanoma in a subject comprising administering an amount of a radiolabeled antimelanin

antibody, wherein the antimelanin antibody is 6D2, does not reasonably provide enablement for a method of treating and/or imaging any and/or all tumors, including melanoma, comprising administering any and/or all radiolabeled antibodies specific for melanin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claims 1-2 read on a method of treating and/or imaging a melanin containing tumor comprising administering a radiolabeled monoclonal antibody which binds to melanin. Thus, claims 1-4 read a method of treating and/or imaging any and/or all melanin containing tumors comprising administering any and/or all radiolabeled monoclonal antibodies specific for melanin. Claims 5-19, 25-33 and 35-37 read on a method of treating and/or imaging a melanin-containing melanoma comprising administering a radiolabeled antimelanin monoclonal antibody. Thus, the claims read on administration of any and/or all radiolabeled antimelanin antibodies.

The scope of the instant claims is not commensurate with the enablement of the instant disclosure, because practice of the claimed invention would require undue experimentation by an artisan of ordinary skill in the art. The instant specification is not enabling for claims drawn to a method of treating and/or imaging any and/or all melanin containing tumors, including melanoma comprising administering any and/or all radiolabeled antibodies specific for melanin. The

specification teaches (page 5, paragraph 0024) that the present invention involves a method of treating and/or imaging tumors in a subject comprising administering a radiolabeled antibody effective to treat or image the tumor, wherein the antibody binds to a cellular component released by a dying tumor cell including, but not limited to, a histone, a mitochondrial protein, a cytoplasmic protein or a pigment, e.g., melanin. With regards to the tumor, the specification teaches (page 6, paragraph 0030) that the term "tumor" includes melanoma. The specification further provides (page 13, paragraph 0055 to 0056 and page 14, paragraph 0059 to 0060) the in vivo binding/distribution of radiolabeled antimelanin antibody 6D2 in melanoma containing mice, as well as the radioimmunotherapy of melanomas using the radiolabeled antimelanin antibody 6D2. Moreover, the specification provides a prospective example (beginning on page 16, paragraph 0067) on how to make and/or use antibodies to human melanin. Thus, while the specification clearly conveys the treatment and/or imaging of melanin containing melanoma's comprising administering radiolabeled 6D2 anti-melanin antibody, the specification appears to be silent on the treatment of any other tumor or the specificity of any other anti-melanin antibody.

The closest prior art to the instantly claimed invention is Mason et al. (Cancer Research 1954; 14; 648-650), whom teaches a radiolabeled anti-melanin antibody (abstract). Specifically, the reference teaches that that administration of a radiolabeled anti-melanin antibody to mice bearing melanin containing melanoma's resulted in no significant localization of radioactivity, wherein the failure to localize may be ascribed to several causes, most likely of which is the relative impermeability of mouse melanoma cells to rabbit antibodies (page 650, 1st column, 1st paragraph to 2nd paragraph).

As such, the instant specification provides insufficient guidance and objective evidence to predictably enable one of skill in the art to use the invention as claimed. Those of skill in the art would recognize the unpredictability of using any radiolabeled antibody to melanin for radioimmunotherapy and/or radio imaging. For example, Wilder et al. (J. Clin. Oncol. 1996; 14: 1383-1400) discloses challenges that currently face radioimmunotherapy (abstract). These challenges include: (1) circulating free antigen, biding of antibodies to nonspecific Fc receptors, insufficient tumor penetration, antigenic heterogeneity and insufficient antigen expression, antigenic modulation and development of human antimouse antibodies. Wilder et al. further teach the importance of dosimetry for treatment planning and assessment of results, wherein dosimetry is dependent on the

kinetics of uptake and clearance of radiolabeled antibodies, the distribution of radiolabeled antibodies and the radioisotope attached to the antibody (page 1387, 1st column, 3rd paragraph from bottom). For example, Wilder et al. teach that the transport of antibodies through the intestinal space of a tumor by diffusion and convection is impeded by antigen binding and relatively large extravascular distances which results in a heterogeneous distribution of antibodies. Along the same lines, Erdi et al. (Phys. Med. Biol. 1996; 41: 2009-20026) disclose that although RIT (radioimmunotherapy) is an innovative and promising approach, there is problems to be solved which limit its use (page 2009, Introduction). These problems include: (1) the low uptake of the radiolabeled antibody; (2) the low target:non-target ratios and the inhomogenous distribution of antibodies within the tumor. While these reference demonstrate the importance of the specificity, uptake and distribution of the antibody in radioimmunotherapy, the same consideration and/or problems associated with RIT are found with radio imaging as well, see for example Chatel et al. (Eur. J. Nucl. Med. 1992; 19: 205-213). More recently, Milenic et al. (Nature Rev. Drug Discovery 3: 488-498, 2004) reviewed antibody-targeted radiation cancer therapy. In particular, Milenic concludes with "[A]fter more than two decades, mAb-targeted therapies are generally recognizes as making a significant impact on cancer therapy.... "[H]owever, despite the wealth of knowledge and capability in antibody engineering, the first two approved radiolabelled mAbs were murine in nature and subject to all of the resultant limitations; that is, immunogenicity and biological half-lives. Knowledge of actual clinical use of radiolabelled mAbs remains in its infancy in many respects, particularly with regards to therapies beyond lympho-haematological diseases, fractionated dosing and the rational construction of drug-combination cocktail therapies to functionally integrate targeted radiation therapy with established therapies and external beam therapies." As such, in view of the teachings of supra, the skilled artisan would not have found sufficient guidance in the specification to achieve an effective method of treating an/or imaging tumors comprising administering any and/or all radiolabeled antibodies to melanin.

In view of the lack of guidance and the large amount of experimentation in an unpredictable art, it would require undue experimentation to practice the claimed invention.

In response to this rejection, Applicants assert that the application provides examples of the invention using a radiolabeled anti-melanin antibody referred to as 6D2, as well as using a radiolabeled anti-melanin peptide 4B4. In addition to the specific examples, Applicants contend that

the application teaches how to prepare and use radiolabeled antibodies starting at paragraph [0067]; and further, additional anti-melanin antibodies have been described in the scientific literature (see for example, Liu and Jimbow (Melanoma Res. 1993; 3: 463-469); Rosa et al. (Infection and Immunity 2000; 68: 2845-2853); and Younchim et al. (J. Medicinal Microbiology 2004; 53: 175-181)). Moreover, Applicants assert that even if the invention as claimed did read on an inoperative embodiment, "the presence of inoperative embodiments with in the scope of the claim does not necessarily render the claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normal required in the art. Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984)" (MPEP 2164.08 (b).

These arguments have been carefully considered, but are not found persuasive.

With respect to Applicants arguments pertaining to the examples in the specification, the Examiner acknowledges and concedes that the specification provides examples of the invention using a radiolabeled anti-melanin antibody referred to as 6D2, as well as a radiolabeled anti-melanin peptide 4B4. However, the Examiner recognizes that the claims are drawn to treating and/or imaging a melanin containing tumor comprising administering a monoclonal antibody which specifically binds to melanin. As such, while the Examiner appreciates Applicants for pointing out the anti-melanin peptide, this example does not appear to be commensurate in scope with the claimed invention which is drawn to immunotherapy and/or immunoimaging, e.g., use of an anti-melanin antibody. Regarding Applicants assertions that the specification teaches how to prepare and use radiolabeled antibodies and further, additional anti-melanin antibodies have been described in the scientific literature, the Examiner acknowledges and appreciates Applicants for pointing out that a variety of anti-melanin antibodies have been described in the scientific literature. However, while the Examiner recognizes that while anti-melanin antibodies have been previously described, the state of the prior art appears to be silent with respect to successfully using radiolabeled anti-melanin antibodies in vivo for imaging or treatment. For example, as noted above, Mason et al. (Cancer Research 1954; 14; 648-650) teaches that administration of a radiolabeled anti-melanin antibody to mice bearing melanin containing melanoma's resulted in no significant localization of radioactivity (page 650, 1st column, 1st paragraph to 2nd paragraph). Finally with respect to Applicants arguments pertaining to inoperative embodiments, the Examiner acknowledges that the presence of inoperative

embodiments within the scope of a claim does not necessarily render a claim non-enabled. However, given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the lack of guidance provided in the specification, and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as written.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 2, 5, 6, 9, 10-11, 14, 16, 19, 33, 35-36 and 41-44 are rejected under 35 U.S.C. 102(a) as being anticipated by Dadachova et al. ("Radioimmunotherapy of Pigmented Melanoma with Melanin-Targeting Antibody," In Program of Ninth Conference on Cancer Therapy with Antibodies and Immunoconjugates, October 22, 2002, Abstract, P-08, IDS).

Dadachova et al. teach a method of treating a subject having a melanin containing tumor, such as a melanoma, comprising administering to the subject a radiolabelled monoclonal antibody which specifically binds to melanin, wherein tumor shrinkage is visible. With regards to the monoclonal antibody, the reference teaches that the monoclonal antibody is a IgM type referred to as 6D2. With regards to the radiolabel, the reference teaches that that radiolabel is ^{188}Re administered at a dose of 1.5 mCi. The reference further teaches a method of imaging a melanin containing tumor comprising administering the monoclonal antibody referred to as 6D2 labeled with gold balls. Thus, while Dadachova *et al.* do not specifically teach the functional characteristics described in claims 33 and 35-36, the claimed functional limitation would be an inherent property of the referenced method since it antibody used by the prior art appears to be identical to a monoclonal antibody referred to in the specification (see for example, paragraph 0054). As such, inherently the antibodies would have the same functional characteristics and therefore, it does not appear that the claim language or limitation results in a manipulative difference in the method steps when compared

to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 7-8, 12-13 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dadachova et al. ("Radioimmunotherapy of Pigmented Melanoma with Melanin-Targeting Antibody," In Program of Ninth Conference on Cancer Therapy with Antibodies and Immunoconjugates, October 22, 2002, Abstract, P-08, IDS) as applied to claims 1, 2, 5, 6, 9, 10-11, 14, 16, 19, 33, 35-36 and 41-44 above, in view of Rodwell et al. (US 5,047,227, 1991).

Dadachova et al. teach a method of treating a subject having a melanin containing tumor, such as a melanoma, comprising administering to the subject a radiolabelled monoclonal antibody which specifically binds to melanin, wherein tumor shrinkage is visible. With regards to the monoclonal antibody, the reference teaches that the monoclonal antibody is a IgM type referred to as 6D2. With regards to the radiolabel, the reference teaches that that radiolabel is ^{188}Re administered at a dose of 1.5 mCi. The reference further teaches a method of imaging a melanin containing tumor comprising administering the monoclonal antibody referred to as 6D2 labeled with gold balls.

Dodachova et al. do not explicitly teach that the radioisotope is an alpha emitter such as 213 Bismuth or that the imaging agent is 99m-Technetium.

Rodwell et al. teach antibody conjugates useful for the treatment of cancers in humans(column 9, lines 6-10). In particular, the patent teaches that antibodies labeled with beta or alpha emitting metal ions such as Bismuth-213 are suitable for therapeutic uses for targeted cell killing, whereas metal ions such as Indium-111, Technetium 99m, Rhenium-186 and Rhenium-188 are useful for diagnosis and imaging sites in vivo (column 9, lines 23-33).

Thus, it would have been prima facie obvious at the time the invention was made to substitute the radioisotopes as taught by Dadachova et al. for the radioisotopes taught by Rodwell et

al. One would have been motivated to do so because each of the radioisotopes have been individually taught in the prior art to be effective at treatment and/or imaging. As such, the equivalency is recognized in the prior art. Thus, one would have a reasonable expectation that by substituting the radioisotopes as taught by Dadachova et al. for the radioisotopes taught by Rodwell et al., one would achieve a method of treating and/or imaging a melanin containing tumor.

Claims 18 and 25-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dadachova et al. ("Radioimmunotherapy of Pigmented Melanoma with Melanin-Targeting Antibody," In Program of Ninth Conference on Cancer Therapy with Antibodies and Immunoconjugates, October 22, 2002, Abstract, P-08, IDS) in view of in view of Rodwell et al. (US 5,047,227, 1991) as applied to claims 1, 2, 5, 6-9, 10-16, 19, 33, 35-36 and 41-44 above, in further view of Kobayashi et al. (Cancer Research 1996; 56: 3788-3795).

Dadachova et al. in view of Rodwell et al. teach a method of treating a subject having a melanin containing tumor such as a melanoma and/or imaging a tumor, such as a melanoma in a patient, comprising administering to the subject a radiolabelled monoclonal antibody referred to as 6D2 which specifically binds to melanin, wherein the radiolabels include, but are not limited to Rhenium 188 or Bismuth 213 for the treatment and/or Indium-111, Technetium 99m, Rhenium-186 or Rhenium-188 for imaging.

Dadachova et al. in view of Rodwell et al. do not explicitly teach that the antibody is a fab' fragment or that the method further comprises administering a positively charged amino acid such as lysine to the subject.

Kobayashi et al. teach that radiolabeled Fab fragments of whole antibodies are better suited for tumor imaging due to their improved kinetics and lower immunogenicity (page 3788, 1st column, 1st paragraph). Kobayashi et al. further teach that although radiolabeled Fab fragments have shown a favorable tumor:nontumor ratios, they have also shown undesirable elevation in renal uptake (page 3788, 2nd column, 1st full paragraph). As a way to circumvent this problem, Kobayashi et al. teach that administration of lysine with or immediately before injection the radiolabeled fragment effectively blocks renal uptake of the fragment (page 3794, 2nd column, last paragraph).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made modify the antibody taught by Dadachova to include Fab fragments and further

to administer lysine with or immediately before the administration of the radiolabeled antibody in view of the teachings of Kobayashi et al. One would have been motivated to do so because Kobayashi et al. teach that radiolabelled Fab fragments of whole antibodies are better suited for tumor imaging due to their improved kinetics and lower immunogenicity and further, that there renal uptake can be eliminated by the administration of lysine. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by modifying the antibody taught by Dadachova to include Fab fragments and further to administer lysine with or immediately before the administration of the radiolabeled antibody in view of the teachings of Kobayashi et al., one would achieve a high tumor to nontumor ratio and avoid renal uptake of the radiolabelled antibody

Therefore, No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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